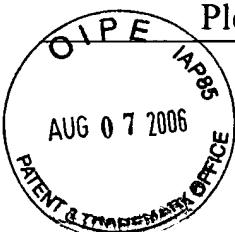


*OAK***Please Direct All Correspondence to Customer Number 30313**

**TRANSMITTAL LETTER**  
**APPEAL BRIEF**

Applicant :	Ashkenazi, et al.
App. No :	10/066,273
Filed :	February 1, 2002
For :	SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME
Examiner :	Chernyshev, Olga N.
Art Unit :	1649

**CERTIFICATE OF MAILING**

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

August 1, 2006

(Date)

AnneMarie Kaiser, Reg. No. 37,649

**Mail Stop Appeal Brief - Patents**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing in the above-identified application are the following enclosures:

- (X) Amended Appellants' Appeal Brief on Appeal to the Board of Patent Appeals and Interferences in forty-four (44) pages.
- (X) Return prepaid postcard.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Dated: August 1, 2006

AnneMarie Kaiser  
Registration No. 37,649  
Attorney of Record  
Customer No. 30,313  
(619) 235-8550

GNE.3130R1C2



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

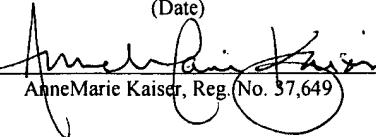
Applicant : Ashkenazi, et al.  
Appl. No. : 10/066,273  
Filed : February 1, 2002  
For : SECRETED AND  
TRANSMEMBRANE  
POLYPEPTIDES AND NUCLEIC  
ACIDS ENCODING THE SAME  
Examiner : Chernyshev, Olga N.  
Group Art Unit : 1649

CERTIFICATE OF MAILING

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August 1, 2006

(Date)

  
AnneMarie Kaiser, Reg. No. 37,649

**AMENDED APPEAL BRIEF**

**ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES**  
**APPELLANT'S BRIEF**

**Mail Stop Appeal Brief – Patents**  
COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

In response to the Notification of Non-Compliant Appeal Brief mailed July 5, 2006, Applicants submit herewith an Amended Appeal Brief. Applicants have removed the subheading "Grouping of the Claims" in Section VI, and have amended the heading titles for Sections VIII to X.

The Applicants appeal the rejection of Claims 40-44 in the above-captioned patent application. These claims were rejected in a final Office Action mailed November 25, 2005. Applicants filed a Notice of Appeal February 24, 2006.

**I. REAL PARTY IN INTEREST**

Pursuant to 37 C.F.R. 41.37(c)(1), Appellants hereby notify the Board of Patent Appeals and Interferences that the real party in interest is the assignee of record for this application, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080.

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**II. RELATED APPEALS AND INTERFERENCES**

Appellants are unaware of any other related appeals or interferences.

**III. STATUS OF THE CLAIMS**

The above-captioned application was filed with Claims 1-39. Appellants cancelled Claims 1-39 and added new Claims 40-45 in a Preliminary Amendment0 mailed February 1, 2001. Appellants canceled Claim 45 in an Amendment and Response mailed July 27, 2004. Appellants amended Claim 40 in an Amendment and Response filed September 1, 2004. The Examiner rejected Claims 40-44 in a final Office Action dated November 25, 2005.

Accordingly, Claims 40-44 are the subject of this appeal. The claims attached hereto as Appendix A reflect the claims as amended by the Amendment filed with the Amendment and Response mailed September 1, 2004.

**IV. STATUS OF AMENDMENTS**

No amendments have been filed subsequent to the issuance of the final Office Action dated January 24, 2006.

**V. SUMMARY OF THE CLAIMED SUBJECT MATTER**

The claimed subject matter relates to antibodies that specifically bind to the polypeptide of SEQ ID NO: 9.

Various aspects of the claimed antibodies are described in the specification at, for example, p. 90, l. 30 through p. 99, l. 6, and Figure 4. SEQ ID NO:9 is disclosed in the Sequence Listing appended to the application.

**VI.  GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL AND GROUPING OF CLAIMS**

**A. Grounds of Rejection on Appeal**

The Examiner has rejected pending Claims 40-44 under 35 U.S.C. §101, stating that the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. *Final Office Action* at 2.

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The Examiner also has rejected pending Claims 40-44 under 35 U.S.C. §112, first paragraph as lacking an enabling disclosure, asserting that “since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility ... one skilled in the art clearly would not know how to use the claimed invention.” *Final Office Action* at 8-9.

## **VII. APPELLANTS’ ARGUMENT**

### **A. Summary of the Arguments**

#### **1. Utility Rejection**

The first issue before the Board is whether Appellants have asserted at least one “specific, substantial, and credible utility” for the claimed subject matter. *See*, Examination Guidelines, 66 Fed. Reg. 1092 (2001). Briefly stated, Appellants’ asserted utility is based on the disclosure in Example 60 of the instant application that the PRO444 polypeptide stimulates *c-fos* expression in retinal pericyte cells. It is well-established that pericyte cells are involved in various stages of angiogenesis, including in the formation of new capillary sprouts, in promoting the survival of newly formed vasculature, and in regulating capillary permeability. Further, it is well established that pericytes secrete VEGF, a well-known potent angiogenic factor, known to be involved in cellular proliferation, survival of newly formed vasculature, and in regulating vascular permeability. Finally, it is known that *c-fos* is a component of the AP-1 transcription factor, and that AP-1 regulates expression of VEGF. The induction of *c-fos* in pericyte cells stimulates VEGF, tying *c-fos* induction in pericyte cells to angiogenesis. Accordingly, PRO444 polypeptides, which Applicants have demonstrated stimulate *c-fos* in pericyte cells, are useful as both therapeutic targets for pathological angiogenesis (*e.g.*, pericyte-associated tumors) and as stimulators of angiogenesis. The claimed antibodies, which specifically bind PRO444 polypeptides, are therefore useful as therapeutic agents. The asserted utilities are specific, substantial, and credible.

#### **2. Enablement Rejection**

The second issue before the Board is whether Appellants have enabled the pending claims such that one of skill in the art would be able to make and use the claimed invention. The

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Examiner has rejected pending Claims 40-44 under 35 U.S.C. §112, first paragraph, arguing that because the claimed antibodies are not supported by either a specific or substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. *Final Office Action* at 9.

Appellants submit that Claims 40-44 are enabled such that one of skill in the art could make and use the claimed antibodies without undue experimentation. Applicants submit that the claimed antibodies have a substantial, specific, and credible utility. Since the enablement rejection is based on the rejection of the claims as lacking utility, the claimed antibodies do not lack enablement.

## **B. Utility Rejection – Detailed Arguments**

The first issue before the Board is whether Appellants have asserted at least one “specific, substantial, and credible utility” for the claimed subject matter. *See Examination Guidelines*, 66 Fed. Reg. 1092 (2001). The Examiner has rejected Claims 40-44 under 35 U.S.C. §§ 101 as lacking utility. Appellants have asserted that the claimed antibodies that specifically bind to the polypeptide of SEQ ID NO:9 (the PRO44 polypeptide) are useful as therapeutic targets for pathological angiogenesis or as tools for stimulating angiogenesis. This asserted utility is specific, substantial, and credible, as is explained in more detail below.

### **1. Utility – Legal Standard**

A “specific utility” is defined as utility which is “specific to the subject matter claimed,” in contrast to “a general utility that would be applicable to the broad class of the invention.” *See M.P.E.P. § 2107.01 I.* For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “[t]he basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the

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claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a ‘substantial’ utility.” *M.P.E.P.* § 2107.01 (emphasis added).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose … and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that “to overcome the presumption of truth that an assertion of utility by the applicant enjoys” the PTO must establish that it is “more likely than not that one of ordinary skill in the art would doubt (i.e., ‘question’) the truth of the statement of utility.” *M.P.E.P.* § 2107.02 III A.

## **2. Utility – Burden of Proof**

It is well established that a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented “must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974). Thus “the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention’s asserted utility. *Id.*

## **3. Utility – Standard of Proof**

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or “more likely

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than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* § 2107.02, part VII (emphasis in original, citations omitted).

The Court of Appeals for the Federal Circuit has stated that the standard for satisfying the utility requirement is a low one:

The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. *See Brenner v. Manson*, 383 U.S. 519, 534, 86 S.Ct. 1033, 16 L.Ed.2d 69 (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end"). *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 U.S.P.Q. 2d 1700 (Fed. Cir. 1999) (emphasis added).

The low threshold for satisfying the utility requirement is reflected in the standard set by the Federal Circuit for invalidating a patent based on a lack of utility: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility. Some degree of utility is sufficient for patentability. Further, the defense of non-utility cannot be sustained without proof of total incapacity." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 U.S.P.Q. 473 (Fed. Cir. 1984) (emphasis added, citations omitted).

Because the standard for satisfying the utility requirement is so low, requiring total incapacity for a finding of no utility, the M.P.E.P. cautions that:

Rejections under 35 U.S.C. 101 have been *rarely* sustained by federal courts. Generally speaking, in these *rare* cases, the 35 U.S.C. 101 rejection was sustained [] because the applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *M.P.E.P.* § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (C.C.P.A. 1967) (underline emphasis in original, italic emphasis added).

4. *Appellants Asserted a Specific, Substantial and Credible Utility that is Sufficient to Satisfy the Utility Requirement of § 101*

The claimed subject matter is directed to antibodies that specifically bind to the polypeptide of SEQ ID NO:9. The polypeptide of SEQ ID NO:9 (referred to as “PRO444 polypeptide”) is encoded by the polynucleotide of SEQ ID NO:8 (also referred to as DNA26846-1397). *Specification*, Example 5. Appellants have asserted that the claimed antibodies are useful in the purification of PRO444 polypeptides, which in turn have utility as both therapeutic targets for tumors associated with pericytes and as stimulators of angiogenesis.

In “Example 60: Pericyte c-Fos Induction” Appellants disclose that the PRO444 polypeptide induces the expression of *c-fos* in pericyte cells at least two fold above a control polypeptide. The specification teaches that induction of *c-fos* expression in pericytes renders the polypeptides “useful. . . as giving rise to antagonists which would be expected to be useful for the therapeutic treatment of pericyte-associated tumors. . .and for the treatment of conditions where induced angiogenesis would be beneficial, including for example, wound healing, and the like.” *Specification* at p. 142, lines 21-27. Example 43 describes purification of PRO polypeptides (e.g., PRO444) using specific antibodies, such as the claimed antibodies. *Specification* at p. 132-133. The specification states that PRO antibodies “can be administered for the treatment of various disorders in the form of pharmaceutical compositions.” *Specification* at p. 97.

Taken together, the specification clearly discloses the use of the claimed antibodies for the purification of PRO444, which has uses both in the isolation of antagonists useful in the treatment of certain tumors, and as a stimulator of angiogenesis where angiogenesis is desirable. These utilities are specific and substantial, as one of skill in the art will recognize that the treatment of certain tumors and the stimulation of angiogenesis are not utilities that apply to the broad class of antibodies; and it is credible, as they not utilities “that could only be true if it violated a scientific principle, . . .or a law of nature, or [is] wholly inconsistent with contemporary knowledge in the art.” M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (C.C.P.A. 1967).

Because Appellants’ specification contains a disclosure of utility which corresponds in scope to the claimed subject matter, the asserted utility “must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re*

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*Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974). Therefore, the burden of establishing a *prima facie* case of lack of utility rests with the PTO. *See, In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) (“the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure”).

#### **5. The Examiner’s Arguments**

In the first Office Action, mailed April 28, 2004, the Examiner rejected the pending claims, stating “Claims 40-45 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility.” *Office Action* mailed April 28, 2004 at 2. This rejection is maintained in the Office Actions mailed September 17, 2004, March 16, 2005, and July 21, 2005, in the final Office Action mailed November 25, 2005, and in the Advisory Action mailed February 7, 2006. *See, Final Office Action* at 2.

To establish a *prima facie* showing that the claimed subject matter lacks utility, the Examiner must “provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The Examiner has issued a total of five Office Actions during the prosecution of the instant application. In these Actions, the Examiner has cited a total of nine references in attempting to provide evidence that one of ordinary skill in the art would reasonably doubt Appellants’ asserted utility. As discussed below, not one of these references provides evidence that one of ordinary skill in the art would reasonably doubt the asserted utilities, and therefore does not establish the requisite *prima facie* showing to support a rejection under 35 U.S.C. § 101.

The Examiner states that the specification discloses that the PRO444 polypeptide acts to induce the expression of *c-fos* in pericyte cells, and that Appellants have asserted the use of the PRO444 polypeptides for giving rise to antagonists which would be expected to be useful for the therapeutic treatment of tumors and for the treatment of conditions where induced angiogenesis would be beneficial. However, the Examiner rejects these utilities, arguing that “the evidence presented. . .is inadequate to support a conclusion that PRO444 induced activation of expression of *c-fos* in pericytes is specifically related to angiogenesis.” *Final Office Action* at 4.

First, the Examiner argues that many growth factors and signals activate *c-fos*, and that the role of *c-fos* is not limited to cancer. Therefore, the Examiner argues that “there appears to

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be no specific biological function that could be particularly attributed to PRO444 with respect to its ability to activate *c-fos* expression in pericytes.” *Office Action* mailed March 16, 2005, at 5 (emphasis added). Six of the nine references cited by the Examiner, Janknecht et al. ((1995) *Carcinogenesis*, 16(3): 443-450), Herrera et al. ((1996) *Prog. Neurobiol.* 50: 83-107), Kováks et al. ((1998) *Neurochem. Int.* 33: 287-297), Coulon et al. ((1999) *J. Biol. Chem.* 274(3): 30439-304346), Sakurai et al. ((2002) *Invest. Opth. Vis. Sci.* 43(6): 2774-2781) and Otani et al. ((2000) *Opth. Vis. Sci.* 41(5): 1192-1199), were cited to support the Examiner’s position that a specific biological function cannot be attributed a compound that induces *c-fos* in pericyte cells, and that as such PRO444 is not useful under 35 U.S.C. § 101. As discussed below, four of these six references that allegedly demonstrate that Appellants’ asserted utilities are not specific to PRO444 do not even concern *c-fos* induction in pericyte cells. Accordingly, these references are irrelevant to Appellants’ asserted utilities, which are based on induction of *c-fos* in pericyte cells, and carry no evidentiary weight in support of the Examiner’s *prima facie* showing. The remaining two references, Sakurai et al. and Otani et al., relate to *c-fos* induction in pericyte cells. As discussed below, the two relevant references provide strong support for Appellants’ asserted utilities.

Second, the Examiner argues that there is “no information at the time of filing regarding pericytes’ specific role in angiogenesis.” *See, e.g., Final Office Action* at 5. The Examiner takes the position that the role of pericytes in angiogenesis is “controversial” and that it is “presently not known whether stimulation of pericytes results in up-regulation or down-regulation of vascularization.” *See, Final Office Action* at 5; *Office Action* mailed July 21, 2005 at 3. The Examiner relies on Diaz-Florez et al. ((1994) *Histol. Histopath.* 9: 807-843) and Ozerdem et al. ((2003) *Angiogenesis* 6:241-249) in support of her position. As discussed below, both Diaz-Florez et al. and Ozerdem et al. demonstrate that pericytes have known, specific roles in angiogenesis. Contrary to the Examiner’s assertions, Diaz-Florez et al. enumerates specific stages in angiogenesis in which it had been previously shown that pericytes play integral roles. Ozerdem et al. not only teaches that pericyte cells are involved in angiogenic sprout formation and migration, but also discloses that pericyte cells are useful for the same asserted utilities asserted by Appellants, namely as “targets for therapeutics for pathological vascularization (*e.g.*, cancer), or as tools to facilitate vascularization (*e.g.*, ischemic disorders).” Ozerdem et al. at 248.

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Finally, the Examiner argues that the relationship between *c-fos*, AP-1 and VEGF expression is “not obvious” and that “there is no evidence that induction of . . .*c fos*. . .leads to stimulation of VEGF by means of. . .AP-1.” *Final Office Action* at 5. The Examiner relies on only one reference, Orlandini et al. ((1996) *Proc. Nat. Acad. Sci. USA* 93: 11675-11680), in support of her position. As discussed below, Orlandini et al. concerns *in vitro* experiments done in fibroblast cells. Orlandini et al. is not probative of *c-fos* regulation in pericytes. Further, the authors themselves caution readers that the reported results are inconsistent with *in vivo* studies that demonstrate *c-fos* regulation of VEGF in association with tumors.

Based on these arguments and cited references, the Examiner argues that “the instant polypeptide PRO444 is suitable only for additional research to identify or reasonably confirm a ‘real world’ context of use.” *Final Office Action* at 8. The Examiner thus concludes that PRO444 and antibodies that bind PRO444 do not have a substantial or well-established utility. *Id.*

**6. The Examiner has not established a Prima Facie case that Claims 40-44 lack Utility**

The above arguments do not satisfy the Examiner’s burden to “provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The Examiner has the burden of presenting “countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant’s assertion of utility.” *M.P.E.P.* at §2107.02 III.A., *citing in re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) (“Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence”) (emphasis added). The Examiner relies on the Herrera et al., Kováks et al., Janknecht et al., Coulon et al., Sakurai et al., Otani et al., Diaz-Florez et al., Ozerdem et al., and Orlandini et al. references to support her arguments. However, for the reasons discussed below, they do not support the Examiner’s position. Therefore, the Examiner’s assertions are not supported by any relevant facts, evidence, or reasoning, and there is simply no evidence in the record to support the Examiner’s arguments that Appellants’ asserted utility is not specific or substantial, and that the invention is incomplete. Absent some relevant evidence to support her assertions, the Examiner

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has failed to establish a *prima facie* showing that one of skill in the art would reasonably doubt the asserted utility, and the Board should accept Appellants' disclosed utility as sufficient.

a. **The data in Example 60 are sufficient to establish a specific asserted utility**

Appellants turn first to the Examiner's arguments that Example 60 does not support a specific utility for PRO444 polypeptides and the claimed antibodies. According to the Examiner, Appellants' evidence of *c-fos* induction in pericytes does not establish "a specific biological role for these protein [sic] . . . or their significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a desired effect," even in light of Appellants' assertion that this activity renders PRO444 useful for treating pericyte-associated tumors or stimulating angiogenesis. *Office Action* mailed April 28, 2004 at 3. According to the Examiner "the art clearly recognizes that induction of *c-fos* expression represents a general non-specific first line of cellular response to a variety of stimuli in a variety of cells [and thus] one skilled in the art would not attribute the induction of *c-fos* in pericytes by the instant polypeptides as a physiological reaction specifically induced by these particular polypeptides." *Office Action* mailed September 17, 2004 at 4. *See also, Final Office Action* at 5 (stating that "*c-fos*. . . is known to be induced by many cellular stimuli, including growth factors, cytokines, T-cell activators, UV irradiation, hypoxia and PMA.")

In the section entitled "Specific and Substantial Requirements" for utility of inventions, the M.P.E.P. states that a specific utility "is specific to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention." M.P.E.P. §2107.02 II(A). The M.P.E.P. instructs Examiners that where an applicant discloses a particular biological activity and reasonably correlates that activity to a disease or condition, the applicant has identified a specific utility for the invention. *Id.* Appellants' specification contains an assertion of utility that meets both of the requirements. Appellants' specification states that "induction of *c-fos* in pericytes is [] indicative of the induction of angiogenesis," and states that this particular biological activity of PRO444 renders those peptides useful as both therapeutic targets for pathological angiogenesis and as stimulators of angiogenesis. *See, Specification*, p. 142, lines 23-25. Accordingly, Appellants have identified a particular biological activity of a compound and explained how that activity can be utilized in a particular therapeutic application

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of the compound, fulfilling the requirements for assertion of a specific and substantial utility for the claimed invention.

In an attempt to clarify to the Examiner that Assay 93 in Example 60 identified compounds with specific activities, Appellants submitted a declaration by Mary Gerritsen, Ph.D. with a Request for Continued Examination on January 18, 2005. Dr. Gerritsen explains that both positive and negative controls were run in Example 60 (Assay 93). Of the 648 samples assayed, only 48 samples, many of which were different lots of the same compound, tested positive for induction of *c-fos* activation in pericytes in Example 60 (Assay 93). Gerritsen Decl., ¶ 10. Dr. Gerritsen's testimony thus establishes that *c-fos* induction in pericytes is not an activity that applies to proteins in general, and likewise that antibodies that bind proteins that induce *c-fos* cannot be a *general* utility that is applicable to the broad class of the invention.

The fact that PRO444 may not be the only factor capable of stimulating *c-fos* does not detract from Appellants' asserted utilities. The Examiner has failed to offer sound reasoning or logic why, based on the fact that various stimuli are known to induce *c-fos*, the skilled artisan would not believe Appellants' that PRO444 induction of *c-fos* in pericyte cells is not a specific biological activity. The Examiner has also failed to offer sound reasoning or logic why the fact that *c-fos* can be induced in neuronal cells or other cells, the skilled artisan would not believe that *c-fos* induction in pericyte cells (specialized cells known to be involved in angiogenesis) is indicative of angiogenesis.

In summary, Appellants' asserted utilities for the claimed antibodies are not "a *general* utility that is applicable to the broad class of the invention." M.P.E.P. §2107.02 II(A). Appellants have described a "specific" utility for the claimed antibodies.

**b. The evidence cited by the Examiner does not refute Appellants' assertion that induction of *c-fos* in pericytes is a physiological reaction specifically induced by PRO444**

Appellants next turn to the evidence cited by the Examiner that demonstrates that *c-fos* is induced by several stimuli, which the Examiner argues establishes that PRO444 polypeptides lack a biological function that could be particularly attributed to PRO444. Appellants discuss below each of the references relied upon by the Examiner in support of her position.

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The Examiner argues that Janknecht et al. demonstrates that “the *c-fos* protooncogene is a member of the immediate-early genes (IEGs), which are rapidly induced upon stimulation of cells with growth factors, cytokines, serum, or UV light.” *Office Action* mailed April 24, 2004 at 3. Janknecht et al. is a general review of the regulatory elements at the *c-fos* promoter. Inasmuch as the teachings of Janknecht et al. are relevant to *c-fos* regulation in any particular cell type, (e.g., pericyte cells), Appellants maintain that the teachings of Janknecht et al. provide strong support for Appellants’ asserted utilities. First, Janknecht et al. teaches that several of the “various stimuli” for *c-fos* noted by the Examiner that induce *c-fos* do so through the Raf-1 pathway. Janknecht et al. at 445. As discussed below, at the time of filing it was known that VEGF was also activated through the Raf-1 pathway, thereby linking many of the “various stimuli” that induce *c-fos* to the induction of VEGF expression, a well-established angiogenic factor. *See*, Kolch et al. (1995) *Breast Cancer Res. Treat.* 36:139-155 at 144-145. Janknecht et al. also teaches that *c-fos* is regulated by the cAMP pathway. cAMP is also known regulator of VEGF expression. *See*, Kolch et al. at 141; Sakurai et al. at 2780. Finally, Janknecht et al. teaches that in 1995 it was well known that *c-fos* regulates cellular proliferation and differentiation. Janknecht et al. at 443. Appellants assertion that *c-fos* stimulation in pericytes is associated with angiogenesis, which involves both cellular proliferation and differentiation, is fully consistent with the teachings of Janknecht et al. In other words, rather than providing any evidence that would lead the skilled artisan to doubt Appellants’ asserted utilities, the teachings of Janknecht et al. weigh strongly in favor of Appellants’ asserted utilities.

In a similar line of reasoning, the Examiner cites to Herrera et al. and Kováks et al. as demonstrating that the disclosure in Example 60 does not provide evidence that PRO444 has a particular, specific activity. *See*, *Office Action* mailed September 17, 2004 at 3-4; *Office Action* mailed April 24, 2004 at 4. According to the Examiner, Herrera et al. and Kováks et al. teach that *c-fos* is induced by neurotropic factors, neurotransmitters, depolarizing agents, or ion channel activating agents. *Office Action* mailed April 24, 2004 at 4.

Herrera et al. is a review article entitled “Activation of *c-fos* in the Brain.” Herrera et al. does not touch on the subject of *c-fos* activation in pericytes and consequently has no bearing on Appellants’ asserted utilities. Interestingly, however, Herrera et al. mentions that studies on *c-fos* activation following brain wounds have led scientists to propose a role for *c-fos* in wound healing in the brain. Herrera et al. at 90. As such, inasmuch as Hererra et al. provides any

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evidence probative of Appellants' asserted utilities, Herrera et al. weighs in favor of Appellants' assertion that PRO444 polypeptides are useful in inducing angiogenesis, for example, in wound healing.

Kováks et al. is yet another review article that describes the role of *c-fos* as a functional marker of activated neurons. Like Herrera et al., Kováks et al. does not touch on the subject of *c-fos* activation in pericytes and consequently has no bearing on Appellants' asserted utilities.

In short, Herrera et al. and Kováks et al. are not relevant to Appellants' asserted utilities and certainly are not sufficient to establish a *prima facie* case of lack of utility under 35 U.S.C. § 101.

The Examiner has also relied upon Coulon et al. for the same proposition described above, *i.e.*, "that induction of *c-fos* can be evoked by a variety of extracellular stimuli." *Office Action* mailed March 16, 2005 at 5. Further, the Examiner asserts that "with respect to the issue of activation of *c-fos* and cell specificity" Coulon et al. "clearly indicate that not only nervous cells but cells of different types response [*sic*] to 'wide range of extracellular stimuli' by activation of immediate early response gene *c-fos*," allegedly demonstrating that *c-fos* induction in pericytes is not associated with a specific or substantial utility. *Office Action* mailed March 16, 2005 at 6. The Examiner argues that these facts show that the disclosure in Example 60 is insufficient to demonstrate that PRO444 has a specific biological function. Coulon et al. is a study conducted on mouse Ltk<sup>-</sup> fibroblast cells. Coulon et al. showed that "calcium ionophore acts in synergy with either cAMP or PMA to strongly induce the endogenous *c-fos* gene." Coulon et al., abstract. As discussed above, Appellants' asserted utilities are based on experiments performed in pericyte cells, specialized cells known to play specific roles in angiogenesis. Coulon et al. concerns a different cell type, *i.e.*, mouse Ltk<sup>-</sup> fibroblast cells. As such, Coulon et al. is not probative of Appellants' asserted utilities. Moreover, cAMP and PMA are well known inducers of VEGF, a potent angiogenic factor. See, Kolch et al. at 141; Balabanov et al. at 640, and references cited therein. Thus, even if Coulon et al. was relevant, the teachings of Coulon et al. are fully consistent with and support Appellants' asserted utilities.

Appellants next turn to the remaining two references relied upon by the Examiner for the proposition that the activity of PRO444 does not support a specific (and presumably substantial) utility, Sakurai et al. and Otani et al. Unlike the evidence discussed above, both Sakurai et al. and Otani et al. concern *c-fos* induction in pericyte cells.

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The Examiner argues that Sakurai et al. teaches that *c-fos* mRNA is induced in pericyte cells by fetal calf serum (FCS) and various prostaglandins, (*i.e.*, PDG<sub>2</sub>) and thus shows that “activation of *c-fos* is a non-specific immediate cellular response to plurality [*sic*] of different factors.” *Office Action* mailed November 25, 2005 at 7. The Examiner later argues that Sakurai et al. teaches that not all inducers of *c-fos* in pericyte cells would be expected to induce angiogenesis. More specifically, the Examiner asserts that Sakurai et al. “describes that the expression of *c-fos* mRNA was induced by FCS (fetal calf serum) and various prostaglandins (see Figure 5); however, only PGD<sub>2</sub> affected the expression levels of VEGF mRNA.” *Id.* (emphasis added). The Examiner asserts that Sakurai shows that the skilled artisan would thus “readily appreciate that disclosure that PRO444 polypeptides are capable of stimulation of *c-fos* does not provide any meaningful or definitive evidence that PRO444 molecules could be used as therapeutics in treatment of pathological angiogenesis or any other clinical conditions.” *Id.* As discussed below, this is an entirely misleading interpretation of Sakurai et al.

Sakurai et al. is a study that examined the role of prostaglandins in proliferative retinopathy, in which “the underlying mechanism. . .is the formation of new vessels.” Sakurai et al. at 2774. The authors hypothesized that prostaglandins, which are well-known inflammatory mediators, may play a role in the development of new vessels. *Id.* To test this hypothesis, the authors examined whether PDG<sub>2</sub> and other prostaglandins for their ability to stimulate proliferation of pericyte cells. As positive and negative controls of pericyte proliferation, the authors cultured pericyte cells in media with or without 10% FCS, respectively. *Id.* at 2775. The authors found that treating pericytes with PDG<sub>2</sub>, as well as PGE<sub>2</sub>, PGF<sub>2α</sub> and FCS (the positive control) induced pericyte proliferation. *Id.* at 2776. The authors next assayed the induction of *c-fos* in pericytes treated with prostaglandins or FCS (positive control) and found that when pericytes were treated with PDG<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2α</sub>, and FCS (positive control), the expression of *c-fos* increased. Moreover, the level of pericyte proliferation correlated with the level of *c-fos* induction. *Id.* at 2777. Because PDG<sub>2</sub> induced pericyte proliferation and *c-fos* expression to the greatest extent, the authors chose PDG<sub>2</sub> as the model to examine whether prostaglandins also induced VEGF expression. *Id.* at 2777-2778. Pericytes treated with PDG<sub>2</sub> showed increased levels of VEGF expression, “a key growth factor in neovascularization.” *Id.* PGD<sub>2</sub> was the only compound that was tested for its effect on VEGF mRNA expression in pericytes.

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Sakurai et al. also teaches that PGD<sub>2</sub> mediates induction of *c-fos* and VEGF through the same pathway. See, Sakurai et al. at Figures 3 and 8. Specifically, Sakurai et al. reported that PGD<sub>2</sub>-mediated induction of *c-fos* is mediated by cAMP. Not surprisingly, a compound that blocks cAMP blocked both PGD<sub>2</sub>-mediated induction of *c-fos* and PDG<sub>2</sub>-mediated induction of VEGF mRNA. This data confirms the teachings of Janknecht et al. and Kolch et al. described above that state that *c-fos* and VEGF are regulated by the same signal transduction pathways. See, Kolch et al. at 141-144; Janknecht et al. at 444-446. Sakurai et al. concluded that their findings provide an explanation “for the known link between angiogenesis and chronic inflammation.” *Id.* at 2780. Notably, the authors referenced Otani et al. (discussed below), and stated that the findings of Sakurai et al together with the findings of Otani et al. “further support the view that [ ] induction of *c-fos* mRNA is an important step in the induction of VEGF expression in retinal pericytes.” *Id.*

The Examiner’s assertions regarding the Sakurai et al. reference are clearly false. The Examiner argues that Sakurai et al. teaches that only a subset of the factors that induce *c-fos* in turn induce expression of VEGF, but fails to mention that the authors did not even examine whether *c-fos* induction by FCS, PGE<sub>2</sub>, or PGF<sub>2α</sub> stimulated VEGF. Therefore, Sakurai et al. provides no evidence that would lead the skilled artisan to believe that PGE<sub>2</sub>, PGF<sub>2α</sub>, and FCS, as stimulators of *c-fos* expression, would not also induce levels of VEGF expression. To the contrary, the one compound tested for both its ability to induce *c-fos* and to induce VEGF showed that induction of *c-fos* correlated with induction of VEGF. Thus, the teachings of Sakurai et al. would lead the skilled artisan to believe that the compounds that were not tested (*i.e.*, PGE<sub>2</sub>, PGF<sub>2α</sub> and FCS) also induce VEGF expression. That this is indeed the case is demonstrated by the teachings of Kolch et al. that “[b]one formation requires angiogenesis and is strongly stimulated by prostaglandins E1 and E2 (PGE). PGE treatment of osteoblasts increases the expression of VEGF mRNA and protein . . . VEGF induction is blocked by cAMP antagonists.” Kolch et al. at 141. Thus, at least one of the compounds discussed in Sakurai et al. falling within the “subset” of compounds that allegedly induce *c-fos* expression but not VEGF expression, is in fact a known inducer of VEGF.

Accordingly, Sakurai et al. does not support the Examiner’s position. To the contrary, Sakurai et al. is strong evidence in support of Appellants’ asserted utilities.

Otani et al. is the only other reference cited by the Examiner in support of her position that induction of *c-fos* in pericytes cannot support a specific (and presumably a substantial) utility. Like Sakurai et al., Otani et al. concerns *c-fos* expression in pericyte cells. The Examiner argues that Otani et al. teach that both angiotensin II (AII) and VEGF activate *c-fos* in pericytes. *Office Action* mailed March 16, 2005 at 5, demonstrating that “no specific biological function [can] be particularly attributed to PRO444 with respect to its ability to activate *c-fos* expression in pericytes.” *Id.* However, Otani et al. not only fails to provide any support for the Examiner’s assertions, but also confirms that induction of *c-fos* in pericyte cells is recognized as useful by those skilled in the art.

Otani et al. is the continuation of a study that analyzed the role of angiotensin II in retinopathy, which, as discussed in Sakurai et al. above, is attributed to pathogenic neovascularization. Retinal microvasculature is comprised of retinal endothelial cells (ECs) and pericyte cells. Otani et al. at 1192. In a previous study, the authors examined the effect of angiotensin II on retinal endothelial cells. In that report, angiotensin II was shown to potentiate VEGF-mediated angiogenic activity of retinal endothelial cells. That study showed that the angiogenic activity was due to angiotensin II-mediated induction of VEGF receptor expression in retinal epithelial cells. *Id.* In that same study, the authors demonstrated that angiotensin II did not stimulate VEGF expression in retinal endothelial cells.

The experiments disclosed in Otani et al. concern whether and how angiotensin II affects VEGF expression in pericyte cells, the other component of retinal vasculature. The authors found that angiotensin II induces a significant increase in VEGF mRNA in pericyte cells in a time and dose-dependent manner. *See*, Otani et al. Figure 1. The increase in VEGF expression was blocked with antisense *c-fos* oligonucleotides, demonstrating that the induction of VEGF was mediated by *c-fos* expression. Thus, Otani et al. is completely contradictory to the Examiner’s assertion that “there appears to be no evidence of record to show that induction of *c-fos* in pericytes is directly and specifically associated with expression of VEGF.” *Final Office Action* at 5. The authors also demonstrated that the culture media from the angiotensin II treated pericytes was capable of stimulating the proliferation of retinal endothelial cells, presumably due to the secretion of VEGF by the treated pericytes. The authors conclude that “[t]hese findings suggest that AII might induce angiogenic activity through a paracrine function of VEGF in retinal microvascular cells.” *Id.* at 1192. Thus, the authors expressly state the link between *c-fos*

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induction in pericytes and stimulation of angiogenesis. The results of these experiments led the authors to suggest that inhibitors of angiotensin might effectively prevent diabetic retinopathy. In other words, due to the specific biological activity of angiotensin II involving induction of *c-fos* in pericyte cells, the authors suggest that antagonists of angiotensin II would be useful for treating pathogenic neovascularization. As such, Otani et al. provides strong evidence that the skilled artisan would believe that PRO444 polypeptides are useful for identifying antagonists to treat pathogenic vascularization, such as pericyte-associated tumors.

c. The evidence cited by the Examiner does not establish that pericytes have no known, specific role in angiogenesis

Appellants turn next to the Examiner's argument that "there appears to be no information available at the time of filing regarding [the] specific role [of pericytes] in angiogenesis (see Applicant's cited art). Moreover. . . the post-filing publication of Ozerdem et al, 2003, clearly indicates that it is presently not fully understood if stimulation of pericytes results in up-regulation or down-regulation of vascularization. . .[and that] the art at the time of invention does no [sic] substantiate the nexus between stimulation of *c-fos* in pericytes and their involvement, positive or negative, in angiogenesis." *Final Office Action* at 4-5.

In the Examiner's own words, "pericytes are reasonably expected to play a significant role in formation of new blood vessels or angiogenesis." *Final Office Action* at 4. Nevertheless, the Examiner argues that Diaz-Florez et al. and Ozerdem et al. demonstrate that angiogenesis and neovascularization are "very complex" and that the "involvement of pericytes in angiogenesis is controversial and not fully understood." *Office Action* mailed July 21, 2005 at 3. The Examiner maintains that in view of the above, *c-fos* induction in pericytes "cannot be specifically associated with onset of cancer or angiogenesis as asserted in the Gerritsen Declaration." *Office Action* mailed March 16, 2005 at 5-6.

Diaz-Florez unambiguously demonstrates that at the time of filing, pericytes had known, specific roles in angiogenesis.

The abstract of Diaz-Florez lists the following "events" in neovascularization:

- a) endothelial cell (EC) *and pericyte activation;*
- b) basal lamina degradation;
- c) *migration and proliferation of EC and pericytes;*
- d) formation of a new capillary vessel lumen;
- e) *appearance of pericytes around the new capillaries;*
- f) development of a new basal lamina;
- g) capillary loop formation;
- h) persistence or involution, and differentiation of the new vessels; and
- i) capillary network

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formation and, eventually, organization into larger microvessels. (emphasis added)

Although Diaz-Florez et al. states that angiogenesis is “complex,” and that “*stepwise*, the current model of angiogenesis is controversial,” Diaz-Florez et al. makes it abundantly clear that at the time the instant application was filed, pericytes were known to be involved in several specific steps of angiogenesis. The passage of Diaz-Florez et al. previously cited by the Examiner as demonstrating that the role of pericytes was “controversial,” states that “*most of the authors* are of the opinion that the involvement of capillaries with pericytes occurs at the end of the proliferative stage,” (*Id.* at 818), which Appellants submit is addressed in studies demonstrating the role of pericytes and VEGF in survival of newly formed vasculature, discussed further below. The “controversy” discussed in Diaz-Florez et al. that the Examiner argues weighs against Appellants’ asserted utilities refers to a discussion of studies that had demonstrated that in addition to their role in the survival of newly formed vasculature, studies had shown that pericytes played an early role angiogenesis. More specifically, the referenced studies showed “fusion of pericytes with the endothelium at the point of active angiogenesis. . .and the presence of cytoplasmic processes of pericytes and EC caving in on each other. . .in the early stages of neovascularization. . .[and] nascent pericytes showing cellular processes advancing at the tips of endothelial sprouts. . .suggesting that pericytes may serve as guiding structures of EC outgrowth.” *Id.* Appellants submit that Diaz-Florez et al. does not provide evidence that would lead the skilled artisan to believe that pericytes have no known, specific, roles in angiogenesis and that weigh against Appellants’ asserted utilities. To the contrary, Diaz-Florez et al. enumerates several specific functions of pericyte cells in angiogenesis such as sprout formation/EC proliferation, and survival of newly formed vasculature. Notably, the Examiner does not address Appellants’ assertions regarding the teachings of Diaz-Florez et al. in the Final Office Action or the Advisory Action.

The Examiner next asserts that Ozerdem et al. clearly indicates that it is “presently not fully understood if stimulation of pericytes results in up-regulation or down-regulation of vascularization.” *Final Office Action* at 4. This is an entirely misleading interpretation of Ozerdem et al.

Ozerdem et al. studied the composition of angiogenic sprouts by immunofluorescence. The authors reported the occurrence of pericyte tubes in early carcinoma tumors, and noted the presence of “entire vessels [that] appear to be composed of pericyte tubes,” and “large numbers

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of individual pericytes invading the tumors.” Ozerdem et al. at 243. Ozerdem et al. also found “the pericytes and endothelial cells are both present at the growing tip of the vascular sprout.” *Id.* This reconfirms the same specific activity of pericytes reported in Diaz-Florez et al. Importantly, the authors concluded that “activated. . .pericytes play an early role in the development of angiogenic sprouts and vessels” and emphasizes “the early participation of pericytes in both physiological and pathological angiogenesis.” *Id.* Ozerdem et al. teaches that “pericytes represent an additional target for treatments designed either to up-regulate (for example in ischemic disorders), or down-regulate (for example in cancer) vascularization.” *Id.* at 248. In other words, rather than providing evidence that establishes that the skilled artisan would doubt Appellants’ asserted utilities, Ozerdem et al. demonstrates *exactly the opposite*, namely that skilled artisans believe that due to their established role in angiogenesis, pericytes are useful in the exact same capacity that Appellants assert in their specification, i.e., as therapeutic targets for treatments where angiogenesis is desirable (ischemia) or where blocking angiogenesis is desirable (cancer). Thus, Ozerdem et al. does not provide evidence to support the Examiner’s *prima facie* showing, but provides strong evidence that that the skilled artisan would believe Appellants’ asserted utilities.

d. The evidence cited by the Examiner does cast doubt on the relationship between c-fos and VEGF

Appellants turn next to the Examiner’s only remaining argument in support of her *prima facie* case of lack of utility: that the relationship between *c-fos* induction and VEGF expression is not “obvious.” The Examiner relies on Orlandini et al. for the proposition that “there is no indication that induction of expression of *c-fos* protooncogene that is known to be induced by many cellular stimuli, including growth factors, cytokines, T-cell activators, UV irradiation, hypoxia and PMA. . .leads to stimulation of VEGF expression by means of AP-1 transcription factor.” *Final Office Action* at 5.

Orlandini et al. describes an *in vitro* differential mRNA screening study conducted on fibroblast cells that differ in the expression of *c-fos*. Inasmuch as Orlandini et al. is completely silent regarding gene expression levels in pericyte cells, it is irrelevant to Appellants asserted utilities. Orlandini et al. showed that after addition of 10% FCS to culture media, VEGF expression was induced in both *c-fos*<sup>-/-</sup> fibroblast cells and *c-fos*<sup>-/-</sup> fibroblast cells engineered to

constitutively express exogenous *c-fos*. In view of the data, the authors merely suggest that *c-fos* may not be necessary for VEGF expression in fibroblasts cultured *in vitro*.

Importantly, in the discussion of the results, the authors refer to a study by Saez et al. that “contrasts with [their] results.” Orlandini et al. at 11680. Saez et al. is an *in vivo* study of tumorigenesis in *c-fos*<sup>-/-</sup> transgenic mice. Saez et al. (1995) *Cell* 87:721-732. Insofar as Saez et al. is not limited to fibroblast cells, Appellants assert that it is more probative of Appellants’ asserted utilities than Orlandini et al. Saez et al. teaches that tumors in transgenic *c-fos*<sup>-/-</sup> mice “show[] very little external vascularization.” Saez et al. at 723. This finding prompted the authors of Saez et al. to examine the mRNA levels of “certain AP-1 regulated genes” in tumors from *c-fos*<sup>-/-</sup> and *c-fos*<sup>+/+</sup> mice, including VEGF. The authors found that VEGF mRNA levels were 5-10 fold lower in the tumors from the *c-fos*<sup>-/-</sup> mice compared to tumors from *c-fos*<sup>+/+</sup> mice, thereby demonstrating that *c-fos* is necessary for the full induction of VEGF and vascularization of tumor cells.

As shown above, Orlandini et al. is insufficient to support a *prima facie* case of lack of utility. First, Orlandini et al. concerns a different cell type than the specialized pericyte cells used in Example 60 of the instant application. Accordingly, Orlandini et al. is irrelevant to Appellants’ asserted utilities and provides no evidentiary weight that the skilled artisan would doubt Appellants’ utilities. Even if Orlandini et al. was relevant to Appellants’ asserted utilities, the authors of Orlandini et al. question their own conclusions about *c-fos* regulation of VEGF in view of Saez et al., which is more probative of Appellants’ asserted utilities. Saez et al. demonstrates the link between *c-fos* induction, VEGF induction, and vascularization of tumors. Thus, the totality of the evidence weighs in favor of Appellants’ asserted utilities.

e. **Conclusion – The Examiner has failed to establish a *prima facie* case that one of skill in the art would doubt Appellants’ asserted utility**

The Examiner has relied on essentially three arguments in rejecting the pending claims for lack of utility. First, the Examiner presents several articles demonstrating that various stimuli induce *c-fos* in various cell types, and argues that in view of these references, the ability to induce *c-fos* in pericytes “does not provide any meaningful or definitive evidence that PRO444 could be used as therapeutics in treatment of pathological angiogenesis or any other clinical conditions.” *Final Office Action* at 7. Second, the Examiner proffers two articles that allegedly demonstrate that the role of pericytes in angiogenesis is not well understood, and argues that the

references show that the skilled artisan would not believe that induction of *c-fos* in pericytes is associated with cancer or the onset of angiogenesis. Finally, the Examiner argues that the connection between *c-fos*, AP-1, and VEGF is “not obvious” relying on Orlandini et al. as support. Appellants have responded to each of these arguments in turn.

Appellants have shown that the data in Example 60 are sufficient to establish that PRO444 is useful in the treatment of certain tumors and as a stimulator of angiogenesis. The Examiner has not provided any relevant reason or evidence for one of skill in the art to doubt the usefulness of PRO444.

Next Appellants have shown that each and every reference relied upon by the Examiner is either irrelevant to Appellants’ asserted utilities or provides further evidence of Appellants’ asserted utilities. First, Appellants have shown that Janknecht et al., Herrera et al., Kováks et al., and Coulon et al. fail to mention pericyte cells or *c-fos* activation in pericyte cells. Thus, they carry no evidentiary weight in establishing a *prima facie* case that the skilled artisan would question the truth of Appellants’ asserted utilities. Moreover, Janknecht et al. establishes that *c-fos* and VEGF are both regulated by the same signals (e.g., through the Ras/Raf-1 and cAMP pathways), and confirms that it was known in the art that *c-fos* is a transcriptional regulator involved in cellular proliferation and differentiation. Herrera et al. propose that *c-fos* is involved in wound healing in the brain. Appellants have shown that the two references relied upon by the Examiner that particularly concern *c-fos* induction in pericytes, Sakurai et al. and Otani et al., teach that *c-fos* induction leads to VEGF expression in pericytes and that antagonists of inducers of *c-fos* in pericytes are useful in treating pathogenic neovascularization, respectively, thereby providing strong evidence in support of Appellants’ utilities. Second, Appellants have shown that Diaz-Florez et al. and Ozerdem et al. both teach that pericytes have known functions in both early and late stages of angiogenesis by promoting cellular proliferation and by facilitating the survival of newly formed vasculature. Finally, Appellants have shown that Orlandini et al. is not probative of Appellants’ asserted utilities since it concerns *c-fos* expression in fibroblast cells and not pericyte cells and that Orlandini et al. explicitly states that *in vivo* studies of Saez et al. directly contradict the conclusions regarding *c-fos* induction of VEGF expression that the authors draw from their own data. Thus, Orlandini et al. is not strong evidence regarding regulation of VEGF expression overall, and provides no evidence regarding VEGF expression in pericyte cells. Notably, Saez et al., which is not limited to fibroblast cells, teaches that *c-fos* correlates with

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increased VEGF mRNA levels in tumors, and that tumors in *c-fos*-deficient mice lack external vascularization. In other words, Saez et al. provides a link between *c-fos* expression, VEGF expression, and vascularization, fully consistent with Appellants' asserted utilities.

Taken together, the Examiner's arguments are not sufficient to satisfy the Examiner's burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The Examiner's arguments are not supported by any substantial relevant evidence or reasoning which explains why one of ordinary skill in the art would reasonably doubt the asserted utility. Therefore, the Board should accept the Appellants' disclosure of utility. *See Ex parte Rubin*, 5 U.S.P.Q. 2d 1461 (Bd. Pat. App. & Interf. 1987) ("There is no factual support in this record for the examiner's questioning of the denaturation test reported in the specification. ... No reason to doubt 'the objective truth' of the asserted utility having been advanced by the examiner, we accept appellant's disclosure of utility corresponding in scope to the claimed subject matter.").

#### **7. Appellants have provided Sufficient Rebuttal Evidence of Utility**

"Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The rebuttal evidence must be sufficient such that when it is considered as a whole, it is more likely than not that the asserted utility is true. *See In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992) (stating that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard). The M.P.E.P. summarizes the standard of proof required:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* § 2107.02, part VII (emphasis in original, citations omitted).

Appellants remind the Board that the Federal Circuit has stated that the standard for satisfying the utility requirement is a low one: "The threshold of utility is not high: An invention is 'useful'

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under section 101 if it is capable of providing some identifiable benefit.” *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 U.S.P.Q. 2d 1700 (Fed. Cir. 1999).

Even if the Examiner has satisfied her burden of presenting a *prima facie* case of lack of utility, Appellants have supplied more than enough rebuttal evidence, such that when considered as a whole, one of skill in the art would conclude that the asserted utility is more likely than not true. Specifically, Appellants have provided evidence that at the time of filing of the instant application, pericytes were known to have specific roles in angiogenesis in both the formation of new blood vessels and the survival of newly formed vasculature. In addition, Appellants have provided evidence demonstrating that at the time of filing of the instant application, VEGF was known to be a potent angiogenic factor involved in both cellular proliferation in connection with neovascularization, as well as survival of newly formed vasculature. Appellants also provided evidence that at the time of filing *c-fos* was well known to function as a component of the AP-1 transcription factor, which was a recognized regulator of VEGF expression. Finally, in addition to the evidence relied upon by the Examiner in which skilled artisans have articulated the very same utilities for regulators of *c-fos* in pericytes as set forth in Appellants’ specification, Appellants have provided evidence that skilled artisans have in fact looked to upstream regulators of VEGF expression similar to PRO444 as targets for blocking angiogenesis in tumor therapy. Therefore, considering the evidence as a whole, one of skill in the art would not doubt that the claimed antibodies are useful as therapeutic targets for pericyte-associated tumors and as stimulators of angiogenesis.

a. **Appellants have established that pericytes have established specific roles in angiogenesis**

As discussed above, the Examiner has not provided any relevant evidence or reasoning that demonstrates that pericytes do not have specific roles in angiogenesis recognized by those skilled in the art. In contrast to this complete lack of relevant evidence on the part of the Examiner, Appellants have submitted several references that pre-date the instant application that discuss specific roles of pericytes in angiogenesis.

Nehls et al. ((1992) *Cell Tissue Res.* 270:469-474) describes pericyte involvement in capillary sprouting during angiogenesis *in situ*. The authors induced angiogenesis in mouse mesentery tissue and used immunofluorescence to identify pericytes. The authors found that

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pericytes were regularly positioned at and in front of the advancing tips of endothelial sprouts, and bridging gaps between the leading edges of endothelial sprouts. The authors concluded that pericytes are involved in capillary sprouting.

Rhodin et al. also found that pericytes are regularly found in association with capillary sprouts. Rhodin et al., (1989), *J. Submicrosc. Cytol. Pathol.* 21:1-34, 12. As such, the results of Rhodin reinforce the conclusions reached by Nehls, *i.e.*, that pericytes are involved in capillary sprouting.

Diaz-Florez et al. is a review article published prior to the filing date of the present application and was originally cited by the Examiner in the Office Action mailed July 21, 2005. Diaz-Florez demonstrates that at the time of filing, pericytes had known, specific roles in angiogenesis. More specifically, Diaz-Florez states that “*most of the authors* are of the opinion that the involvement of capillaries with pericytes occurs at the end of the proliferative stage,” (*Id.* at 818), which Appellants submit is addressed in studies demonstrating the role of pericytes in survival of newly formed vasculature, discussed further below. Diaz-Florez also addresses studies that show that pericytes play an early role angiogenesis. Other studies referred to in Diaz-Florez showed “fusion of pericytes with the endothelium at the point of active angiogenesis. . .and the presence of cytoplasmic processes of pericytes and EC caving in on each other. . .in the early stages of neovascularization. . .[and] nascent pericytes showing cellular processes advancing at the tips of endothelial sprouts. . .suggesting that pericytes may serve as guiding structures of EC outgrowth.” *Id.* In the final Office Action, the Examiner does not address Appellants’ assertions regarding the specific teachings of Diaz-Florez.

In addition to these references, Appellants previously submitted review articles by Balabanov et al. and Ellis et al. that summarize what was known at the time the instant application was filed regarding the role of pericytes in angiogenesis. Balabanov et al. was published four months after the filing date of the instant application, and echoes the teachings of Nehls et al., Rhodin et al. and Diaz-Florez et al., above, stating:

[p]ericytes have been implicated in all three stages of new vessel formation: 1) initiation, 2) sprout extension and migration, 3) maturation and cessation of growth. (Hirshi and D’Amore, 1997) At the initiation phase pericytes respond to a number of angiogenic stimuli. As a result, they undergo activation, degrade the basement membrane, and migrate out of the microvessels. (Diaz-Florez et al., 1994). Pericytes guide the migrating endothelial cell, regulate their proliferation, and form connections between newly formed sprouts (Hirshi and D’Amore, 1997; Diaz-Florez et al., 1994; Nehls et al., 1992). Such functions are thought to be

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mediated through TGF $\beta$ -1 (Orlidge and D'Amore, 1987; Sato and Rifkin, 1989), vascular endothelial growth factor (Hirshi and D'Amore, 1997, Kim et al., 1998). Balabanov et al. at 640.

Each and every reference cited within Balabanov et al. in the passage above was published prior to Appellants' filing date.

Ellis et al. is yet another review article concerning the role of pericytes in angiogenesis as it relates to tumor biology. Ellis, (2002), *Oncology* 16(5):14-22. Ellis explains that "the tumor microenvironment is a caustic one. . .[t]herefore, for these fragile endothelial cells [that represent the new primitive capillary network] to survive, they must be exposed to endothelial cell survival factors. . .Endothelial cell survival factors include pericytes that may stabilize endothelium. . .by secretion of endothelial cell survival factors such as VEGF." Ellis, at 20. As such, Ellis et al. underscores the fact that it was known that one of the roles in angiogenesis that pericytes play is to promote survival of newly formed vasculature by secreting VEGF.

Finally, Ozerdem et al., entitled "Early contribution of pericytes to angiogenic sprouting and tube formation," is a publication that was originally cited by the Examiner in the Office Action dated March 16, 2005 for the proposition that pericytes "role in formation of tumor neovasculature is currently not fully understood and varies depending on type of tissue and tumor (see page 241, 242, and 246)." To further refine studies regarding the role of pericytes in vascularization of tumors, Ozerdem et al. utilized immunofluorescence to analyze the composition of angiogenic sprouts. The authors found the occurrence of pericyte tubes in early carcinoma tumors, noting the presence of "entire vessels [that] appear to be composed of pericyte tubes," and "large numbers of individual pericytes invading the tumors." Ozerdem et al. at 243. Ozerdem et al. also found "the pericytes and endothelial cells are both present at the growing tip of the vascular sprout." *Id.* The authors conclude that "activated. . .pericytes play an early role in the development of angiogenic sprouts and vessels." and emphasize the early participation of pericytes in both physiological and pathological angiogenesis. *Id.* These findings and conclusions reinforce the findings and conclusions in the earlier studies of Nehls, Rhodin and the studies discussed in Diaz-Florez et al. and Balabanov et al. Even further, Ozerdem et al. provides the suggestion that, due to their specific roles in angiogenesis, "pericytes represent an additional target for treatments designed either to up-regulate (for example in ischemic disorders), or down-regulate (for example in cancer) vascularization." *Id.* at 248. This unambiguously demonstrates that the skilled artisan would believe Appellants' asserted utilities.

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Finally, Appellants previously submitted a Declaration by Dr. Mary Gerritsen as evidence in support of the asserted utilities. Dr. Gerritsen testifies that “pericytes help regulate capillary permeability and stabilize newly formed blood vessels” and that “pericytes play an important role in regulating angiogenesis.” (Gerritsen Decl., ¶6). The pre-filing publications of Nehls et al., Rhodin et al. and Diaz-Florez et al., the pre-filing publications referenced in Balabanov et al., as well as Ellis et al. and Ozerdem et al. all illustrate the same, specific roles for pericytes in angiogenesis testified to by Dr. Gerritsen. The Examiner has offered no reasoning or evidence that contradicts Appellants’ evidence, including the teachings of the references discussed above and Dr. Gerritsen’s testimony, or establishes that the skilled artisan would have a legitimate basis to doubt the credibility of Dr. Gerritsen’s testimony.

The Examiner’s assertion that “there appears to be no information available at the time of filing of [pericyte’s] specific role in angiogenesis,” (*Final Office Action* at 4) is incorrect in view of the evidence discussed above. In fact, all of the evidence of record concerning pericytes demonstrates that at the time the instant application was filed, pericytes were known to be involved in angiogenesis in at least two capacities: endothelial sprout formation and survival of newly formed vasculature.

**b. Appellants have established that VEGF has an established role in angiogenesis**

Appellants next turn to the second portion of their argument in support of their asserted utility – that VEGF has well-established roles in angiogenesis, both in inducing cellular proliferation and vascular permeability, and in promoting survival of newly-formed vasculature. In the section above, Appellants provided several pre-filing references that demonstrated that these same activities are mediated by pericyte cells.

At the time of filing of the instant application, studies had demonstrated that VEGF is involved in survival of endothelial cells in newly formed vessels. Alon et al., (1995), *Nat. Med.* 1(10):1024-1028, examined the role of VEGF in retinopathy of prematurity (ROP), a disorder that ultimately results in blindness. It was generally accepted at the time that VEGF caused the abnormal vasoproliferation in ROP. Alon et al. showed that the absence of VEGF during the early stage in ROP resulted in blood vessel regression. Exogenously added VEGF reversed this

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process. Thus, Alon et al. concluded that VEGF is involved in survival of newly formed vasculature.

The studies of Benjamin et al. (1997), *Proc. Nat. Acad. USA* 94:8761-8766, confirm the role of VEGF in survival of newly-formed vasculature reported in Alon et al. Benjamin et al. engineered tumor cells in which VEGF expression could be induced or shut off. These cells were then injected into mice to study the effects of VEGF expression on tumor vascularization. Not surprisingly, the authors found that over expression of VEGF results in tumor hypervasularity. On the other hand, when VEGF expression was shut off, preformed tumor vessels regressed. Benjamin et al. concluded “VEGF is required for maintenance of . .tumor vessels.” *Id.* at 8762. In a section entitled “Clinical Implications of Vascular Regression Caused by VEGF Withdrawal,” Benjamin et al. state that the “finding that newly formed or remodeling blood vessels require sustained VEGF levels will be critical in the success of many angiogenic and anti-angiogenic therapies.” *Id.* at 8675.

Appellants also submitted Ferrera et al. ((1995) *Breast Cancer Res. and Treat.* 36:127-137) as evidence demonstrating the involvement of VEGF in inducing cellular proliferation involved in angiogenesis. Ferrera et al. cite several references showing that “VEGF is a potent mitogen. . .for vascular endothelial cells.” *Id.* at 128. Ferrera et al. also reference early studies demonstrating that VEGF promotes angiogenesis in a tridimensional *in vitro* model, inducing confluent microvascular endothelial cells to invade a collagen gel and form tube-like structures. *Id.* In addition, Ferrera et al. teaches that it was known that VEGF promotes vascular permeability for vascular endothelial cells. Ferrara, et al. at 127. Ferrera et al. teaches that prior to 1995, VEGF was thought to function in a paracrine fashion. Ferrera et al., at 128. Notably, the study of Otani et al., submitted by the Examiner, confirms the earlier teachings of Ferrara et al., stating that “VEGF. . .produced by pericytes, induce[s] endothelial cell growth in a paracrine manner indicat[ing] a proliferative effect of pericytes.” Otani et al., at 1197.

Appellants submit that the references cited above demonstrate that at the time the Application was filed, those skilled in the art appreciated the critical role of VEGF in angiogenesis, as required for inducing proliferation of vascular endothelial cells, survival of newly formed vasculature, and vascular permeability. This led Kolch et al. to describe VEGF as “the pivotal mediator of pathophysiological angiogenesis.” Kolch et al. at 139. The Examiner has not offered any evidence that calls into question Applicants’ assertions.

The Examiner has conceded that “the role of angiogenic [sic] factor VEGF is well established.” *Final Office Action* at 5. The Examiner has also conceded that “[t]here is also no dispute that the art at the time of filing discloses that pericytes could secrete VEGF.” *Id.* Nevertheless, the Examiner maintains that “the art at the time of the invention does no [sic] substantiate the nexus between stimulation of *c-fos* in pericytes and their involvement, positive or negative, in angiogenesis.” *Office Action* at 5. Appellants submit that the totality of the evidence clearly demonstrates the relationship between VEGF expression and the role of pericyte involvement in angiogenesis. As discussed below, Appellants have also provided several references demonstrating that *c-fos* is a known regulator of VEGF expression.

c. Appellants have established that *c-fos* stimulates VEGF expression

Appellants next turn to the final portion of their argument in support of their asserted utility - that at the time of filing, *c-fos* was known to be part of transcription factor AP-1, and that AP-1 was known to regulate VEGF expression.

The evidence submitted by the Examiner demonstrates that at the time of filing, it was well known that *c-fos* is a component of the AP-1 transcription factor. Citing to a textbook on transcriptional regulators, Janknecht teaches that “the *c-fos* gene encodes a basic region-leucine zipper transcription factor that requires heterodimerization with a member of the Jun family for stable DNA binding. Fos/Jun heterodimers are present in the AP-1 transcription factor.” Janknecht at 443. Thus, there is a clear, “obvious” relationship between *c-fos* and AP-1.

Appellants previously submitted Tischer et al. (1991), *J. Biol. Chem.* 266(18):11947-11954; Shima, et al., (1996) *J. Biol. Chem.* 271(7):3877-3882, 3882; and Kolch et al. as evidence that at the time of filing, AP-1 was known to regulate VEGF expression.

In 1990, Tischer et al. analyzed the human gene for VEGF. Tischer et al. (1991), *J. Biol. Chem.* 266(18):11947-11954. The authors found that the promoter region for hVEGF contains several AP-1 binding sites, suggesting that *c-fos* is a regulator of VEGF expression. Tischer at 11953. Similarly, the structure of the mouse VEGF gene revealed “multiple consensus binding sites for AP-1.” Shima, et al., (1996) *J. Biol. Chem.* 271(7):3877-3882, 3882. In Kolch’s review “Regulation of the expression of the VEGF/VPS and its receptors: role in tumor angiogenesis,” Kolch summarizes the state of the art in 1995 stating that “[a]t present, a comprehensive assessment of several studies highlights the AP-1 transcription factor as an important

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**common denominator for the regulation of VEGF expression.” Kolch, at 144, emphasis added.**

The art available at the time of filing demonstrates that *c-fos* and VEGF are regulated through the same signal transduction pathways, explaining the fact that regulators that function to stimulate *c-fos* also stimulate VEGF expression. More particularly, Kolch et al. highlights various pathways in which both *c-fos* and VEGF expression are regulated, including through the Ras/Raf pathway. *Id.* at 144-145. Janknecht et al. teaches that the Ras/Raf-1 pathway is involved in regulation of *c-fos* by both growth factors and UV light. Janknecht et al. at 444-445. Importantly, Kolch et al. also links the induction of *c-fos* expression through the Raf and Ras pathways with conversion to a tumorigenic phenotype through activation of VEGF. *Id.* at 145. Janknecht et al. also teaches that *c-fos* is regulated by cAMP. As discussed above, Kolch et al. and Sakurai et al. both teach that VEGF is regulated by cAMP. Kolch et al. at 141; Sakurai et al. at 2780. Thus, in view of the fact that the same pathways regulate both *c-fos* and VEGF, the Examiner’s assertions that since growth factors and UV light induce *c-fos*, the skilled artisan would not believe Appellants’ asserted utilities are not convincing. Rather, in view of Janknecht et al. and Kolch et al., the skilled artisan would be led to believe that more likely than not, the same stimuli would also induce VEGF expression. Thus, the literature at the time of filing establishes the link between *c-fos* regulation and VEGF regulation.

Appellants also previously submitted a review article by McColl et al. which articulates Appellants’ reasoning regarding the specificity of molecules such as PRO444 in the following statement: “since *fos* is upregulated by [various stimuli including growth factors], VEGF expression could also be elevated in response to these stimuli, *as is indeed the case.*” McColl et al., (2004) APMIS 112:463-480, 467 and references cited therein (emphasis added).

Appellants submit that the references discussed above demonstrate that at the time the instant application was filed, those skilled in the art appreciated the role of *c-fos* in VEGF expression, and hence, the role of *c-fos* in the angiogenic process, including neovascularization and stabilization of newly formed vasculature.

d. **Appellants have established that skilled artisans believe that indirect regulators of angiogenic factors are useful as therapeutic targets for cancer therapy**

As Dr. Gerritsen testified, “a skilled artisan would reasonably conclude that neutralizing compounds capable of stimulating *c-fos* expression in pericytes (*e.g.*, PRO444) could be useful in preventing the onset and/or progression of cancer and/or angiogenesis.” Gerritsen Decl., ¶6. The numerous references of record that are discussed above fully support this proposition. As even further proof of this principle, however, Appellants previously submitted a review article entitled “Synopsis of Angiogenesis Inhibitors in Oncology.” Ellis et al., (2002) *Oncology* 16(5):14-22. Ellis et al. teaches that in 2002, scientists had proposed and had been working towards developing anti-angiogenic therapies for the treatment of cancer that fell into four different categories: (1) those that decrease the activity of specific angiogenic factors; (2) those that decrease the activity of endothelial survival factors; (3) those that increase the activity of naturally occurring anti-angiogenic agents; and (4) those that indirectly downregulate activity of angiogenic and survival factors. Ellis et al. at 18 (emphasis added). For the purposes of discussion in the review, Ellis et al. use VEGF as “the prototype molecule used to describe strategies to decrease the activity of angiogenic factors.” *Id.* In the discussion of the second strategy, Ellis et al. states that “[e]ndothelial cell survival factors include pericytes that may stabilize endothelium. . .by secretion of endothelial cell survival factors such as VEGF.” In other words, Ellis et al. teaches that by 2002, skilled artisans had been looking to factors that regulate VEGF expression in pericyte cells as cancer therapeutics. Furthermore, in the discussion of the fourth strategy, Ellis et al. states that “strategies that downregulate the upstream signaling pathways to VEGF. . .may indirectly downregulate VEGF activity and angiogenesis.” *Id.* at 20. At the time of filing, it was known that *c-fos* represented an upstream signaling pathway to VEGF. *See*, Kolch et al. 145. As such, Ellis et al. teaches that by 2002, skilled artisans had been looking at factors to downregulate molecules such as *c-fos* as cancer therapeutics. Ellis et al. provides direct evidence that demonstrates that skilled artisans had actually contemplated the use of upstream regulators of VEGF (*e.g.*, PRO444) to identify antagonists for use in cancer therapy.

As even further proof of Appellants’ asserted utilities, Appellants also previously submitted evidence demonstrating that that the first strategy proposed by Ellis, *i.e.*, directly targeting or neutralizing the activity of angiogenic factors such as VEGF, has been demonstrated to be effective. A VEGF-specific antibody, bevacizumab, has been successfully used to treat several cancer types. *See*, Kirkpatrick, P., (2005), *Nat. Rev. Drug Disc.* S8-S9. Willett et al. report that bevacizumab has antivascular effects in human rectal cancer. Willett et al. (2004)

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*Nature Medicine*, 10(2):145-147. Regardless of their publication date, Ellis et al. Kirkpatrick, and Willet et al. summarize years of study involving the identification of regulators of VEGF as cancer therapeutics, and each is irrefutable proof of the truth of Appellants' asserted utilities.

**e. Conclusion**

As a whole, the evidence of record establishes that skilled artisans more likely than not believe that pericyte cells function in angiogenesis by inducing proliferation of vascular endothelial cells and promoting survival of newly formed vasculature; that VEGF is a potent angiogenic factor that induces proliferation of vascular endothelial cells and promotes survival of newly formed vasculature; and that *c-fos* is directly involved in VEGF expression, particularly in pericyte cells. Given the overwhelming amount of evidence in support of Appellants' position, including publications that expressly articulate Appellants' asserted utilities, and the near absence of any relevant evidence in support of the Examiner's position, when considered as a whole, the evidence leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.

**8. The Examiner's Response to Appellants' Evidence is Insufficient to Rebut Appellants' Arguments**

The Examiner has concluded that the teachings of the specification, the scientific references, the declaration of Dr. Gerritsen, and supporting arguments provided by Appellants are not persuasive. *See, e.g., Final Office Action at 8.*

**a. The Examiner's Response to the Nehls, Rhodin, Diaz-Florez, Balabanov and Ellis references**

Appellants submitted several references including Nehls et al., Rhodin et al., Diaz-Florez et al. Balabanov et al., and Ellis et al. as evidence that prior to the filing date of the instant application, those skilled in the art appreciated the specific roles of pericytes in angiogenesis as both stimulators of endothelial cell proliferation and as mediators of survival of newly formed vasculature. In response to Appellants' evidentiary showing, the Examiner states:

Beginning at page 7 of the Response, Applicant submits that at the time of the filing, the role of pericytes in angiogenesis was fully established and refers to articles by Nehls et al., Phodin et al. [sic] and Ozerdam et al. [sic] (the last cited by the Examiner in the previous office action of record). First, it is important to clarify that the Examiner never disputed that pericytes have a role in angiogenesis. Anatomically, as part of vasculature, pericytes are reasonably expected to play a

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significant role in formation of new blood vessels or angiogenesis. However, *there appears to be no information available at the time of filing regarding their specific role in angiogenesis* (see Applicant's cited art). Moreover, information presented in post-filing publication of Ozerdem et al., 2003, clearly indicates that it is presently not fully understood if stimulation of pericytes results in up-regulation or down regulation of vascularization (middle at page 8 of the Response). More importantly, the art at the time of invention does not [sic] substantiate the nexus between stimulation of *c-fos* in pericytes and their involvement, positive or negative, in angiogenesis (see specifically Applicant's reasoning on pages 10-11 of the Response). *Final Office Action*, at 4-5 (emphasis added).

As an initial matter, Appellants' Response to Office Action never alleged that the role of pericytes in angiogenesis was "fully established." Rather, Appellants stated that the several references "illustrat[e] the state of the art regarding pericyte control of angiogenesis at the time the application was filed." *Amendment and Response to Office Action* mailed October 18, 2005. As described above, Nehls et al., Rhodin et al., and Diaz-Florez et al. are each references published prior to Appellants' effective filing date that enumerate specific functions of pericyte cells in angiogenesis (e.g., proliferation and survival of newly formed vasculature). Without addressing the contents of these references, the Examiner makes the conclusory statement that "there appears to be no information available. . .regarding [pericyte's] specific role in angiogenesis." *Final Office Action* at 4.

The Examiner is silent regarding Appellants' assertions regarding the teachings of Diaz-Florez et al., originally submitted by the Examiner in support of her assertion that "the art teaches that process [sic] angiogenesis or neovascularization is controversial and not fully understood." *Office Action* mailed July 21, 2005 at 3.

The Examiner also fails to specifically address Balabanov et al. As Appellants pointed out in the Amendment and Response filed on October 15, 2005, Balabanov et al. is a review article that summarizes the state of the art at the time the instant application was filed. Balabanov et al. was received for publication in June 1998, a mere four months prior to Appellants' priority date of October 28, 1998. In the *Amendment and Response* mailed October 18, 2005, Appellants cited to a passage in Balabanov et al. that in turn cites to several pre-filing references that enumerate the specific roles of pericytes in angiogenesis and attribute several of the specific angiogenic functions of pericytes to the secretion of VEGF. Although the Examiner fails to mention Balabanov et al., assuming that the Examiner's dismissal of this reference as

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evidence is based on the publication date of Balabanov et al., Appellants maintain that the Examiner's failure to consider the evidence is without merit.

As discussed above, the Examiner never fairly addressed Appellants' citation to the Ozerdem et al. reference (originally cited by the Examiner) as evidence that supports rather than disproves Appellants' asserted utilities. As discussed above, Ozerdem et al. reconfirms the teachings of Nehls et al. and Rhodin et al. demonstrating that pericytes are present at the tips of angiogenic sprouts, conclude that "activated. . .pericytes play an early role in the development of angiogenic sprouts and vessels," and underscore the early participation of pericytes in both physiological and pathological angiogenesis. In response, the Examiner mischaracterizes Appellants' citation of Ozerdem et al., making the misleading assertion that "information presented in post-filing [*sic*] publication of Ozerdem et al., 2003, clearly indicates that it is presently not fully understood if stimulation of pericytes results in up-regulation or down-regulation of vascularization." *Final Office Action* at 5. Surprisingly, the Examiner maintains this position in the Advisory Action even after Appellants pointed out that the Examiner mischaracterized or misinterpreted the reference and that Ozerdem et al. teaches that, like Appellants have asserted, depending on the type of disorder (*e.g.* ischemia or cancer), the skilled artisan would recognize that pericytes are useful targets to either induce or inhibit vascularization.

Finally, the Examiner dismisses the publication of Ellis et al., stating that "with respect to the publications used in discussion on pages 12-13 (including Ellis et al.), Applicant is advised that the asserted utility cannot be relied upon disclosure [*sic*] available after the filing date of the instant specification. As with Balabanov et al., Ellis et al. is a review article that summarizes the state of the art as reflected by several studies published to date, many of which, as Appellants' have pointed out, pre-date the filing date of the instant application.

**b. The Examiner's Response to the Alon, Ferrera, Pepper, and Benjamin, References**

Appellants submitted the Alon et al., Ferrera et al., Benjamin et al., and Pepper et al. references as evidence that at the time of filing, VEGF was a well-known angiogenic factor that has biological activities such as inducing proliferation of endothelial cells, promoting survival of endothelial cells, and inducing vascular permeability - specific activities that were attributed to pericyte cells at the time of filing of the instant application.

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In response to Appellants' evidentiary showing, the Examiner concedes that "the role of VEGF is well established. There is also no dispute that the art at the time of filing discloses that pericytes could secrete VEGF." *Final Office Action* at 5.

**c. The Examiner's Response to the Tischer, Shima, Kolch and Janknecht References**

Appellants submitted the Tischer et al., Shima et al., Kolch et al. and Janknecht et al. references as evidence that at the time of filing, the skilled artisan appreciated that *c-fos* is a subunit of AP-1, a known regulator of VEGF expression. In response to Appellants' evidentiary showing, the Examiner states:

Applicant argues at pages 11-12 that because *c-fos* encodes a subunit of the nuclear transcription factor AP-1 and because AP-1 plays a role in the expression of VEGF, then *c-fos* stimulates VEGF expression. Applicant's arguments as well as presented articles by Tischer et al., Shima et al., and Kolch have been fully considered but are not persuasive **because the relationship between *c-fos*, AP-1 and VEGF expression is not obvious**. Applicant's reasoning lacks support in the specification as originally filed and also in the publications of record because there appears to be no indication that induction of expression of *c-fos* protooncogene that is known to be induced by many cellular stimuli, including growth factors, cytokines, T-cell activators, UV irradiation, hypoxia and PMA (see reasoning in the previous office actions of record and also Orlandi [sic] et al, 1996, Proc. Natl. Acad. Sci., USA, Vol. 93, pp. 1675 [sic]-11680) leads to stimulation of VEGF expression by means of AP-1 transcription factor. On the contrary, Orlandi [sic] et al. publication discloses that, for example, in fibroblasts VEGF expression is unaffected by *c-fos*. *Final Office Action* at 7 (emphasis added).

As demonstrated above, the Examiner has offered no reasoning or evidence that contradicts Appellants' evidentiary showing of Janknecht et al. that *c-fos* is a subunit of the AP-1 transcription factor. The Examiner has offered no reasoning or evidence that contradicts Appellants' evidentiary showing of Tischer et al. and Shima et al. that the regulatory region of the VEGF gene contains AP-1 binding sites. As such, the skilled artisan would believe that inducers of *c-fos* would in turn induce VEGF expression. Appellants have provided evidence that establishes that *c-fos* and VEGF are in fact regulated by the same signal transduction pathways, e.g., Ras/Raf-1 and cAMP, and that *c-fos* functions to induce VEGF expression. The only evidence offered by the Examiner to contradict Kolch et al., which states that "a comprehensive assessment of several studies highlights the AP-1 transcription factor as an important common denominator for the regulation of VEGF expression," is an article by

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Orlandini et al. As discussed above, Orlandini et al. is not contradictory to Appellants' evidence. Orlandini et al. is a study done in fibroblast cells, and therefore has no bearing on the regulation of VEGF expression in pericyte cells. Furthermore, Orlandini et al. call into question this very conclusion in view of the evidence that *c-fos* regulates VEGF expression *in vivo*.

**d. The Examiner's Response to the Gerritsen Declaration**

Appellants submitted a declaration under 37 C.F.R. § 1.131 by Dr. Mary Gerritsen as evidence that the compounds identified in Example 60, e.g., PRO444, have a specific biological activity, and that induction of *c-fos* in pericytes is not a generalized response. Dr. Gerritsen's testimony was also provided as evidence that pericytes are unique cells that have specific roles in angiogenesis, including both the stabilization of newly formed blood vessels and the regulation of capillary permeability.

In response to Dr. Gerritsen's testimony, the Examiner states that "the Declaration of Gerristen represents Dr. Gerritsen's own conclusions with no references to scientific publications." *Office Action* mailed March 16, 2005 at 4. According to the Examiner, the testimony in the Gerritsen declaration further establishes that "there appears to be no specific biological function that could be particularly attributed to PRO444 with respect to its ability to activate *c-fos* expression in pericytes," and that "there appears to be no clear physiological meaning attributed to the activation of *c-fos* by PRO444 at the time of filing." *Id.* at 5-6. In the final Office Action, the Examiner maintains that "the Declaration is insufficient to overcome the instant rejection because it does not provide support for the relationship between expression of *c-fos* in pericytes and angiogenesis." *Final Office Action* at 6.

Appellants maintain that the Examiner has not heeded the admonition that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." M.P.E.P. § 2107. In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *See in re Alton* 76 F.3d 1168 (Fed. Cir. 1996). As an initial matter, Appellants have submitted 15 references in addition to the several references cited by the Examiner, which confirm the testimony of Dr. Gerritsen and provide evidence of the truthfulness of Appellants' assertions. These references confirm Dr. Gerritsen's testimony that "retinal pericytes are unique cells that play an important role in. . . angiogenesis. . .[by] regulat[ing] capillary permeability and stabiliz[ing] newly formed blood

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vessels.” Gerritsen Decl. ¶6. *See, e.g.*, Balabanov et al.; Alon et al.; Benjamin et al.; Ferrera et al. The evidence of record, including Janknecht et al., Kolch et al, and McColl et al., also confirms Dr. Gerritsen’s testimony that “C-fos transcription factor is involved in the regulation of cellular growth, including cancer and angiogenesis. Growth factors capable of stimulating pericytes signal through the *c-fos* pathway.” Gerritsen Decl. ¶6. *See, e.g.,* Further, Ozerdem et al., Ellis et al., Sakurai et al, Otani et al. each provides evidence that supports Dr. Gerritsen’s testimony that “a skilled artisan would also conclude that neutralizing compounds capable of stimulating *c-fos* expression in pericytes (*e.g.*, PRO444) could be useful in preventing the onset and/or progression of cancer and/or angiogenesis.” Gerritsen Decl. ¶7. On the other hand, the Examiner has offered no significant reason or evidence to reject the Gerritsen Declaration, and, therefore, there is nothing in the record to controvert these statements of the Gerritsen declaration.

**e. Conclusion - the Examiner's arguments are not persuasive**

In conclusion, Appellants have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because PRO444 polypeptides induce *c-fos* in pericyte cells, PRO444 polypeptides are useful as targets for pericyte-associated tumors, and as stimulators of angiogenesis. This activity of the PRO444 polypeptide makes the antibody that specifically binds to it useful for purification of PRO444, and as a potential antagonist of PRO444. The references and declaration proffered by Appellants clearly support their asserted utility, and the Examiner has offered no relevant arguments or evidence to the contrary. In short, none of the Examiner’s responses to Appellants’ supporting evidence are sufficient to rebut Appellants’ asserted utility.

**9. Utility – Conclusion**

Appellants’ asserted utilities for the claimed antibodies as useful in the isolation of PRO444 polypeptides to be used as targets for therapeutics useful in the treatment of pericyte-associated tumors and as simulators of angiogenesis correspond in scope to the subject matter sought to be patented and therefore “must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject.” *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974). The Examiner’s unsupported arguments and largely irrelevant references are not sufficient evidence to make a *prima facie* showing that “one of ordinary skill in the art

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would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Even if the Examiner has established a *prima facie* case, Appellants have offered sufficient rebuttal evidence in the form of expert declarations and references, which, when considered as a whole, establish that it is more likely than not that the asserted utility is true. *See In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992) (stating that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or “more likely than not” standard); *M.P.E.P.* at § 2107.02, part VII (“evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.”) (emphasis in original). Considering the evidence as a whole, the Board should find that Appellants have established at least one specific, substantial, and credible utility, and the Examiner’s rejection of Claims 40-44 under 35 U.S.C. §§ 101 as lacking utility should be reversed.

#### **C. Enablement Rejection – Detailed Argument**

The second issue before the Board is whether Appellants have enabled the pending claims such that one of skill in the art would be able to make and use the claimed invention. The Examiner has rejected pending Claims 40-44 under 35 U.S.C. §112, first paragraph, arguing that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention. *See final Office Action* at 9. For the reasons provided above, Appellants submit that Appellants have established at least one specific, substantial, and credible utility, and the Examiner’s rejection of Claims 40-44 under 35 U.S.C. § 112, first paragraph, as lacking utility should be reversed.

#### **D. Conclusion**

In view of the arguments presented above, Appellants submit that the specification as filed provides a specific, substantial and credible utility for the claimed antibodies, and, therefore, the claimed subject matter also is enabled. Appellants therefore respectfully request that the Board reverse the rejections of the pending claims as lacking utility under 35 U.S.C. §101, and as not being enabled under 35 U.S.C. §112, first paragraph.

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Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Aug. 1, 2006

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**VIII. CLAIMS APPENDIX**

40. An antibody that specifically binds to the polypeptide of SEQ ID NO:9.
41. The antibody of Claim 40 which is a monoclonal antibody.
42. The antibody of Claim 40 which is a humanized antibody.
43. The antibody of Claim 40 which is an antibody fragment.
44. The antibody of Claim 40 which is labeled.

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**IX. EVIDENCE APPENDIX**

Attached hereto is a copy of the evidence cited in Appellants' Brief. The list of evidence below is accompanied by a statement setting forth where in the record that evidence was entered into the record by the Examiner.

<b>Tab</b>	<b>Reference</b>	<b>Submitted</b>	<b>Entered</b>
1	Kováks <i>et al.</i> (Neurochem. Int., (1998) 33:287-297)		Cited by the Examiner in the Office Action dated 4/28/04
2	Herrera <i>et al.</i> (Prog. Neurobiol., (1996) 50:83-107)		Cited by the Examiner in the Office Action dated 4/28/04
3	Janknecht <i>et al.</i> (Carcinogenesis, (1995) 3:443-450)		Cited by the Examiner in the Office Action dated 4/28/04
4	Saez <i>et al.</i> (Cell., (1995) 82(5):721-732)	Originally submitted with Appellants' Amendment and Response to Office Action mailed 7/27/04	Considered by the Examiner in the Office Action mailed 7/21/05
5	Marconcini <i>et al.</i> (Proc. Nat. Acad. Sci. USA (1999) 96(17):9671- 9676)	Originally submitted with Appellants' Amendment and Response to Office Action mailed 7/27/04	Considered by the Examiner in the Office Action mailed 7/21/05
6	Declaration by Mary Gerritsen, Ph.D.	Originally submitted with Appellants' Amendment and Response to Office Action mailed 1/18/05	Considered by Examiner in Office Action mailed 3/16/05
7	Coulon <i>et al.</i> (J. Biol. Chem. (1999) 274(43):30439-30446)		Cited by the Examiner in Office Action mailed 3/16/05
8	Sakurai <i>et al.</i> , (Invest. Ophthal. and Vis. Sci. (2002) 43(8):2774- 2781)		Cited by the Examiner in Office Action mailed 3/16/05
9	Otani <i>et al.</i> (Invest. Ophthal. and Vis. Sci. (2000) 41(5):1192- 1199)		Cited by the Examiner in Office Action mailed 3/16/05
10	Ozerdem <i>et al.</i> (Angiogenesis (2003) 6:241-249)		Cited by the Examiner in Office Action mailed 3/16/05

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11	McColl <i>et al.</i> , (APMIS (2004) 112:463-480)	Originally submitted with Appellants' Amendment and Response to Office Action mailed 6/15/05 as Exhibit A	Considered by Examiner in final Office Action mailed 7/21/05
12	Diaz-Florez <i>et al.</i> (Histol. Histopath. (1994) 9:807-843)		Cited by the Examiner in final Office Action mailed 7/21/05
13	Alon <i>et al.</i> (Nature Med. (1995) 1(10):1024-1028)	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
14	Benjamin <i>et al.</i> (Proc. Nat. Acad. Sci. USA (1997) 94:8761-8766)	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
15	Ellis, <i>et al.</i> (Oncology (2002) 16(5) Supp. 14-22)	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
16	Ferrera <i>et al.</i> (Breast Cancer Res. Treat. (1995) 36:127-137	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
17	Fidler <i>et al.</i> (Cancer J. (2000) 6(Supp. 3):S225-236)	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
18	Kirkpatrick, P. (Nature (2005) S8-S9)	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
19	Kolch <i>et al.</i> (Breast Cancer Res. Treat. (1995) 36:139-155	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
20	Nehls <i>et al.</i> (Cell Tiss. Res. (1992) 270:469-474)	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
21	Rhodin <i>et al.</i> (J. Submicsosc. Cytol. Pathol. (1989) 21(1):1-34)	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
22	Shima, <i>et al.</i> (J. Biol. Chem. (1996) 271(7):3877-3883)	Originally submitted with Appellants' Submission with Request for Continued	Entered by Examiner in final Office Action mailed 11/25/05

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Examination mailed 10/18/05			
23	Tischer, <i>et al.</i> (J. Biol. Chem. (1991) 266(18):11947-11954)	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
24	Willett, <i>et al.</i> (Nat. Med. (2004) 10(2):145-147)	Originally submitted with Appellants' Submission with Request for Continued Examination mailed 10/18/05	Entered by Examiner in final Office Action mailed 11/25/05
25	Orlandini <i>et al.</i> (Proc. Nat. Acad. Sci. USA (1996) 93:11675-11780)		Cited by the Examiner in final Office Action mailed 11/25/05

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**X. RELATED PROCEEDINGS APPENDIX**

There are no decisions rendered by a court or the Board in any related proceedings identified above.

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